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Remote Control of Intact Mammalian Brain Circuits Using Pulsed Ultrasound

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W911NF-09-1-0431

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER
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6. AUTHORS
William J. Tyler and Brian H. Smith

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAMES AND ADDRESSES
Arizona State University
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Arizona Board of Regents for Arizona State University
Tempe, AZ 85287 -6011

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14. ABSTRACT
We have demonstrated that pulsed ultrasound can stimulate cortical motor circuits, as well as subcortical hippocampal circuits in intake mice. The most important aspect of our work is that we have begun to gain an understanding of what properties of ultrasound waveforms make them effective for neuromodulation. The next phase of translations will include attempting to stimulate sensory regions of the brain, such as somoatosenosry cortex and auditory cortex. In parallel, we are working towards using ultrasound for cognitive modification in

15. SUBJECT TERMS
brain, ultrasound, stimulation

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	15. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			Brian Smith
UU	UU	UU	UU		19b. TELEPHONE NUMBER: 480-326-5524

Report Title

Remote Control of Intact Mammalian Brain Circuits Using Pulsed Ultrasound

ABSTRACT

We have demonstrated that pulsed ultrasound can stimulate cortical motor circuits, as well as subcortical hippocampal circuits in intake mice. The most important aspect of our work is that we have begun to gain an understanding of what properties of ultrasound waveforms make them effective for neuromodulation. The next phase of translations will include attempting to stimulate sensory regions of the brain, such as somoatosenosry cortex and auditory cortex. In parallel, we are working towards using ultrasound for cognitive modification in behaving animals. We anticipate there will be future growth in the use of ultrasound for neuromodulation based in part upon our advancements made. We expect an additional one or two manuscripts will be published in the upcoming year which were partially supported by this grant.

Enter List of papers submitted or published that acknowledge ARO support from the start of the project to the date of this printing. List the papers, including journal references, in the following categories:

(a) Papers published in peer-reviewed journals (N/A for none)

Received		Paper
04/26/2012	1.00	Yusuf Tufail, Anna Yoshihiro, Sandipan Pati, Monica M Li, William J Tyler. Ultrasonic neuromodulation by brain stimulation with transcranial ultrasound, Nature Protocols, (09 2011): 1453. doi: 10.1038/nprot.2011.371
04/26/2012	2.00	William J Tyler. Noninvasive neuromodulation with ultrasound? A continuum mechanics hypothesis., The Neuroscientist, (02 2011): 25. doi:
TOTAL:	**2**	

Number of Papers published in peer-reviewed journals:

(b) Papers published in non-peer-reviewed journals (N/A for none)

Received		Paper
TOTAL:		

Number of Papers published in non peer-reviewed journals:

(c) Presentations

4. Translational Studies Investigating the Modulation of Brain Circuits by Pulsed Ultrasound, Southeastern Veterinary Neurology Conference, October, 2012 – Blacksburg, VA
3. Trials and Tribulations of Building a Neurotrechnology Platform and Company, Invited Speaker, SIPS Intellectual Property Awareness Conference, Virginia Tech, October, 2012 – Blacksburg, VA
2. Ultrasonic Neuromodulation, invited speaker at Medtronic, Inc., August, 2012 – Minneapolis, MN
1. Noninvasive neuromodulation in psychiatric treatment and research, Virginia Tech Carilion School of Medicine, Department of Psychiatry and Behavioral Medicine Grand Rounds, August, 2012 – Roanoke, VA

Number of Presentations: 4.00

Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received	Paper

TOTAL:

Number of Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received	Paper

TOTAL:

Number of Peer-Reviewed Conference Proceeding publications (other than abstracts):

(d) Manuscripts

Received		Paper
12/31/2012	3.00	William Tyler. The mechanobiology of brian function, Nature Reveiws Neuroscience (02 2012)

TOTAL: **1**

Number of Manuscripts:

Books

Received Paper

TOTAL:

Patents Submitted

Patents Awarded

Awards

McKnight Technological Innovation in Neuroscience Award – 2012 – 2014

Graduate Students

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Names of Post Doctorates

NAME	PERCENT_SUPPORTED
Wynn Legon	0.10
FTE Equivalent:	**0.10**
Total Number:	**1**

Names of Faculty Supported

NAME	PERCENT_SUPPORTED	National Academy Member
William Tyler	0.20	
FTE Equivalent:	**0.20**	
Total Number:	**1**	

Names of Under Graduate students supported

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Student Metrics

This section only applies to graduating undergraduates supported by this agreement in this reporting period

The number of undergraduates funded by this agreement who graduated during this period:	0.00
The number of undergraduates funded by this agreement who graduated during this period with a degree in science, mathematics, engineering, or technology fields:.....	0.00
The number of undergraduates funded by your agreement who graduated during this period and will continue to pursue a graduate or Ph.D. degree in science, mathematics, engineering, or technology fields:.....	0.00
Number of graduating undergraduates who achieved a 3.5 GPA to 4.0 (4.0 max scale):	0.00
Number of graduating undergraduates funded by a DoD funded Center of Excellence grant for Education, Research and Engineering:	0.00
The number of undergraduates funded by your agreement who graduated during this period and intend to work for the Department of Defense	0.00
The number of undergraduates funded by your agreement who graduated during this period and will receive scholarships or fellowships for further studies in science, mathematics, engineering or technology fields:	0.00

Names of Personnel receiving masters degrees

NAME
Total Number:

Names of personnel receiving PHDs

NAME
Monica Li
Total Number: 1

Names of other research staff

NAME	PERCENT_SUPPORTED
Aaoron Barbour	0.10
Amanda Williams	0.10
FTE Equivalent:	**0.20**
Total Number:	**2**

Sub Contractors (DD882)

1 a. Virginia Polytechnic Institute & State University

1 b. Office of Sponsored Programs
460 Turner Street, Suite 306
Blacksburg VA 24060

Sub Contractor Numbers (c):
Patent Clause Number (d-1):
Patent Date (d-2):
Work Description (e):
Sub Contract Award Date (f-1):
Sub Contract Est Completion Date(f-2):

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1 a. Virginia Polytechnic Institute & State University

1 b. Office of Sponsored Programs
1880 Pratt Drive, Suite 2006
Blacksburg VA 24060

Sub Contractor Numbers (c):
Patent Clause Number (d-1):
Patent Date (d-2):
Work Description (e):
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Sub Contract Est Completion Date(f-2):

Inventions (DD882)

Scientific Progress

The primary objective of this proposal has been to develop methods for controlling the activity of intact brain circuits using ultrasound. Below an update of our scientific progress towards this objective is outlined.

We initiated a series of investigations aimed at developing noninvasive brain stimulation methods employing ultrasound.

We indeed developed and reported on methods for intact brain circuit stimulation. We found and reported that transcranial pulsed ultrasound can stimulate brain circuits with a spatial resolution approximately five times better than other noninvasive state-of-the-art brain stimulation methods such as TMS and tDCS (Tufail et al., 2010). We additionally showed our method of brain stimulation using transcranial ultrasound is safe, reliable, and temporally precise. In addition, we revealed that pulsed ultrasound is capable of remotely stimulating synchronous brain activity patterns known as sharp-wave ripples in the intact hippocampus, which are known to underlie certain cognitive abilities such as memory trace formation. These data also demonstrate that pulsed ultrasound can stimulate subcortical circuits in the intact rodent brain, as well as superficial cortical circuits.

The studies above have served the foundation for the next phase of experiments for which funding is presently being sought. An original aim of the proposed work was to stimulate sensory regions of the intact mammalian brain. Using funding from other sources, but knowledged gained on intact rodents in the ARL funded work effort we have been able to validate some of our prelimiary findings in larger animal models. We are still attempting to fully understand the exact ultrasound waveforms parameters, which make neuromodulation reliable. We have planned a next series of studies, which is based upon findings made during the ARL work efforts on this grant. We anticipate continued development of ultrasonic neuromodulation for the modulation of sensory brain regions to continue in large animal models.

We recently published an opinion paper in Nature Reviews Neuroscience on the mechanical features of the brain in an article entitled "The Mechanobiology of Brian Function" (Tyler, 2012). In this opinion article, we discuss several aspects of the brain where mechanical forces are known to regulate endogenous function. During our work efforts on the ARL grant, we have proposed that the mechanical pressure source of ultrasound is capable of exerting its actions on these mechanically sensitive features of neurons, glia, and brain circuits to alter activity. We will continue to work on deciphering the exact mechanisms of action by which ultrasound works to influence changes in neuronal activity. Knowledge gained here will lead to the refinement of ultrasonic neuromodulation and its applications in regulating brain activity.

Overall, we have been able to make significant headway in the development of pulsed ultrasound for the noninvasive stimulation of intact brains through the support of our ARO RDECOM ARL grant. We look forward to continued support from the DoD, as well as to be able to help meet some of the needs of our national defense and warfighters through our work.

Technology Transfer